



Spinal Muscular Atrophy as a Focus Indication for Biomarker Development

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Spinal Muscular Atrophy Foundation

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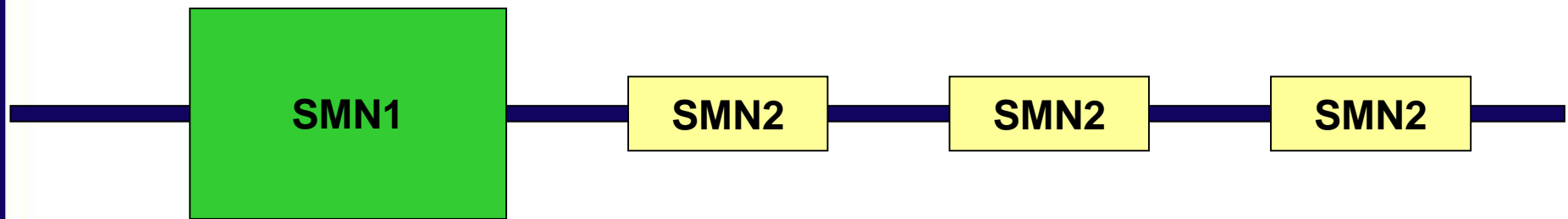
Why SMA?

- ⌘ Low incidence, but a large orphan indication
- ⌘ Scientifically tractable
 - ⌘ Disease gene identified, proposed treatments under investigation
- ⌘ Lessons applicable to other neuro/muscular diseases
- ⌘ Significant groundwork in place
 - ⌘ NIH attention: NINDS SMA Project, NPTUNE clinical network
 - ⌘ Advocacy groups organizing families, research, clinical resources
 - ⌘ International Coordinating Committee for SMA Clinical Trials
 - ⌘ Standards of Care, Outcome Measures, Protocol Design, Biomarkers, etc
 - ⌘ Increasing basic and clinical research momentum
- ⌘ Needs a larger scale effort to assure success
 - ⌘ Need for industry involvement, collaborative efforts

SMA: Leading Genetic Cause of Mortality in Infants and Toddlers

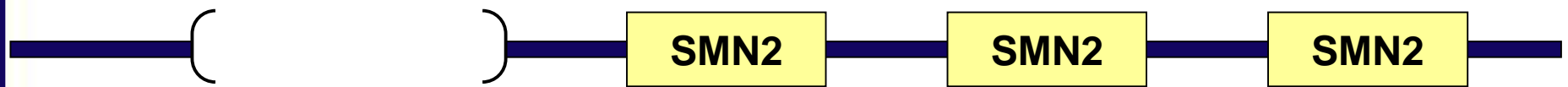
- Ⓟ Severe congenital neurological disease
- Ⓟ Autosomal recessive inheritance; all racial and ethnic groups
- Ⓟ 1 in 35 people (7 million Americans) are carriers
- Ⓟ 1 in 6,000-10,000 incidence
- Ⓟ Well-defined patient population: 50,000+ in US/EU/Japan
- Ⓟ **Common** rare disease: comparable to Cystic Fibrosis, Duchenne Muscular Dystrophy, Sickle Cell Anemia, and ALS
- Ⓟ Foresee a sizable market
 - Ⓝ Enough to provide significant revenues even without ‘homerun’ treatments
 - Ⓝ Disease modifying drugs could produce revenues of **\$500 million to \$1 billion+** per year

SMA Disease Gene Identified



- ⌞ Tandem array of genes
- ⌞ Nearly the same coding sequence, produce different amounts of protein due to splicing defect in SMN2

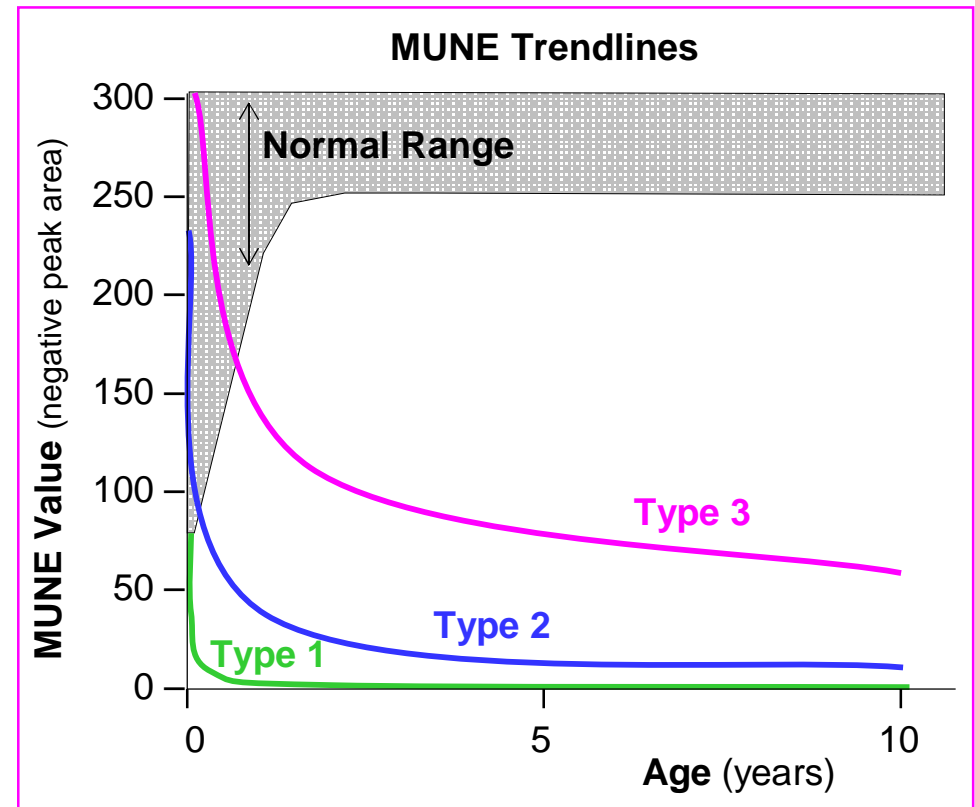
SMA Disease Gene Identified



- Tandem array of genes
- Nearly the same coding sequence, produce different amounts of protein due to splicing defect in SMN2
- Disease occurs when SMN1 is deleted or mutated
- Disease severity, age of onset correlates roughly with SMN2 copy number

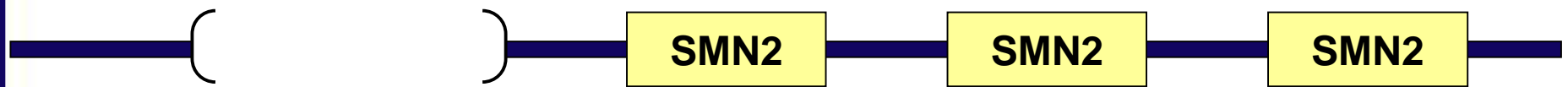
Natural History: Hope for Treatment

- Motor neurons present and functional
 - Motor neurons persist after MUNE counts decline
- Number of functional motor units (MUNE scores) correlates with disease severity
 - Evidence for reinnervation in Type 2 and 3 disease
- Strong expectation that raising SMN expression should offset disease**



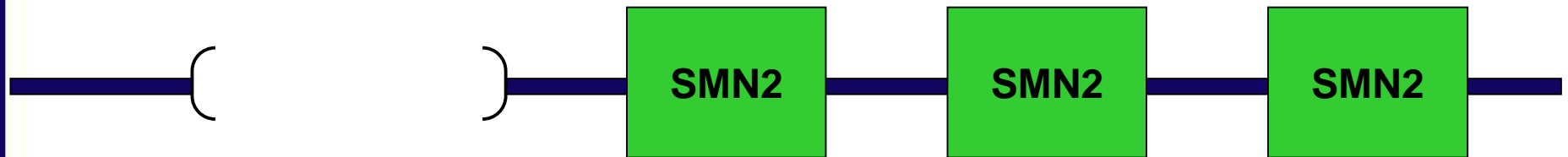
Based on Swoboda et al (2005) Ann Neurol 57:704-712

SMN Expression Can Be Increased



- ⌘ Early findings in patient fibroblast and lymphoblastoid cells
 - ⌘ Phenylbutyrate, Valproate, Hydroxyurea now being pursued clinically

SMN Expression Can Be Increased

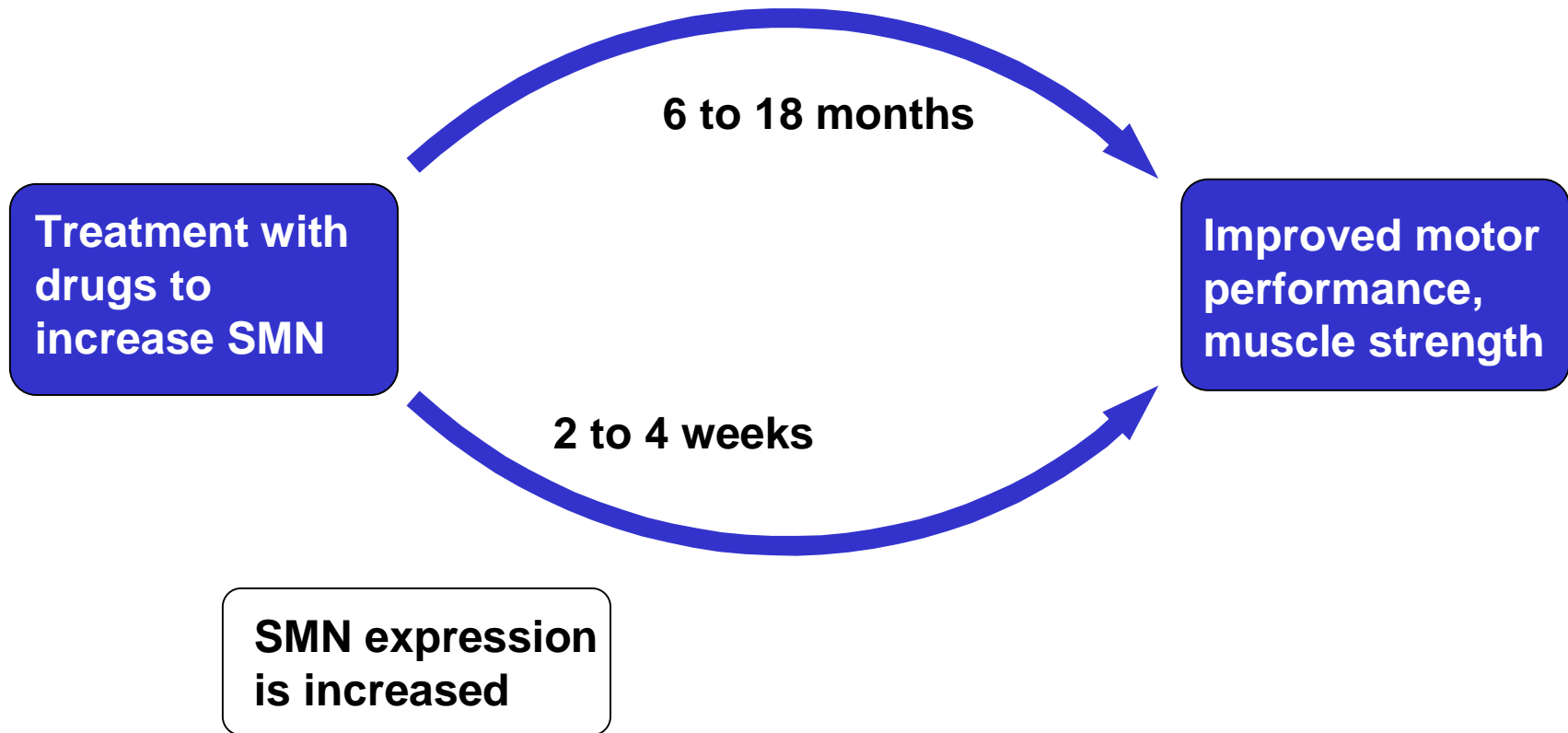


- ⌘ Early findings in patient fibroblast and lymphoblastoid cells
 - ⌘ Phenylbutyrate, Valproate, Hydroxyurea now being pursued clinically
- ⌘ “Biotech” discovery and development efforts
 - ⌘ NIH and Foundations
 - ⌘ IND’s expected in 2007, 2008+
- ⌘ Proof of concept in mice for HDAC inhibitors
 - ⌘ Butyrate: Tsai et al (2006) Neurobiol Dis
 - ⌘ Trichostatin: Avila et al (2007) J Clin Invest
- ⌘ Clinical studies underway

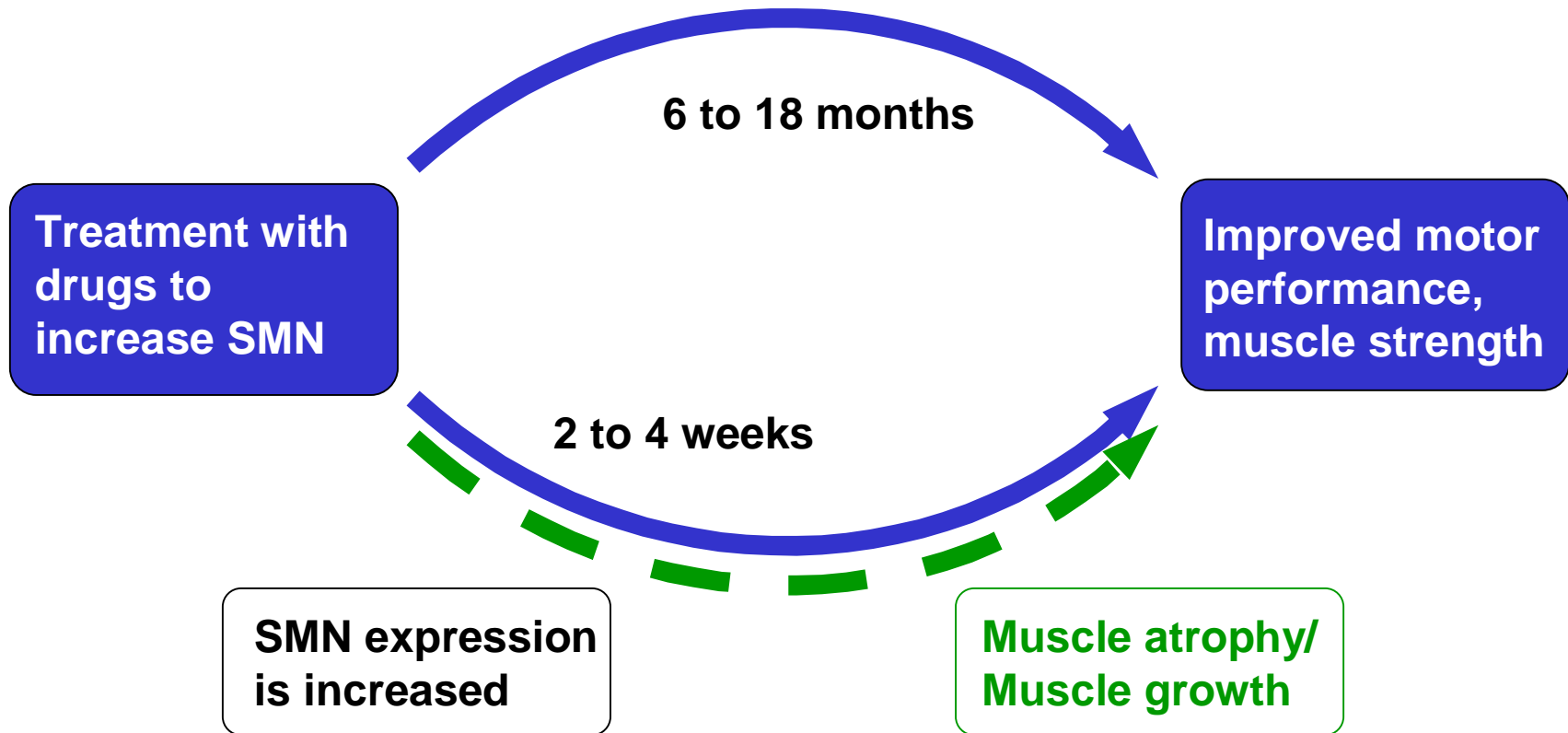
SMA Clinical Landscape

- Ⓟ Investigator-driven, open-label studies showed modest benefit
- Ⓟ Placebo-controlled studies directed at SMN expression
 - Ⓝ First controlled trial: Mercuri et al, 2007, Neurology
 - Ⓝ Others underway, e.g. CARNI-VAL (Project Cure); Stanford HU pilot
 - Ⓝ No industry-sponsored trials yet announced
- Ⓟ Trial design
 - Ⓝ Typically several months of treatment time
 - Ⓝ Outcomes: motor function, pulmonary function, time to event (survival)
- Ⓟ Potential impact of a biomarker
 - Ⓝ Shorter, smaller trials especially in Phase II
 - Ⓝ Reduce barrier to entry for biotech/pharma (Phase 0)

Clinical Hypothesis



Clinical Hypothesis



SMN Measurements

p Several labs developing methods for blood samples

n *Brahe et al, 2004, Eur J Hum Gen*

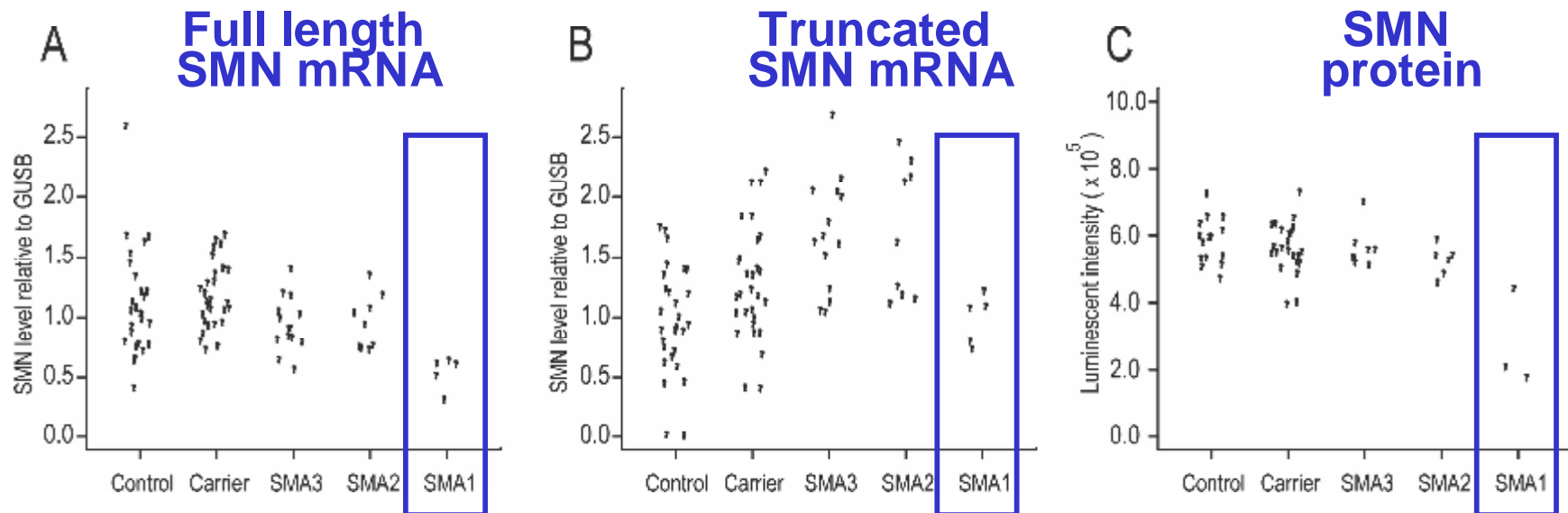
n *Sumner et al, 2006, Neurology*

n *Brichta et al, 2006, Ann Neurol*

n *Simard et al, 2007, Neurology*

p Stable baseline for SMN protein and transcript

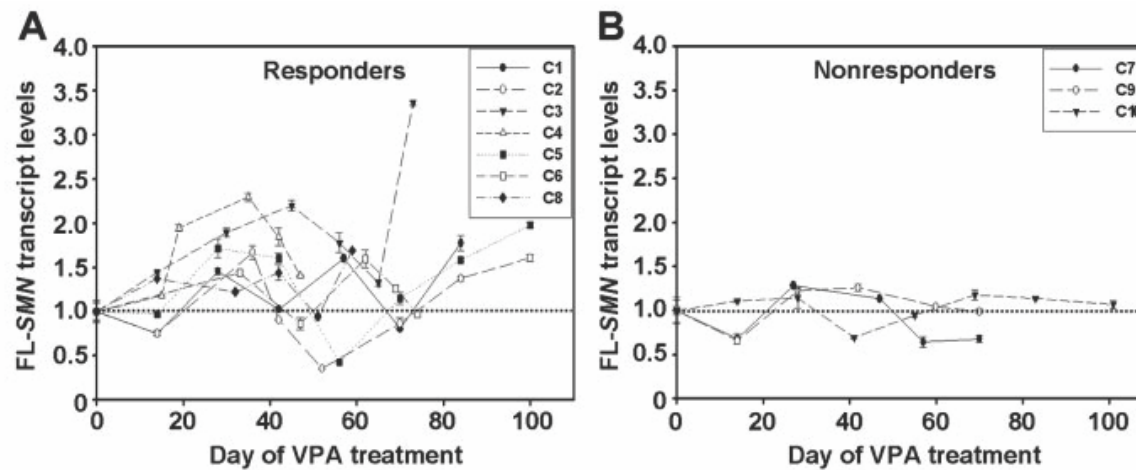
p Overlap between clinical types



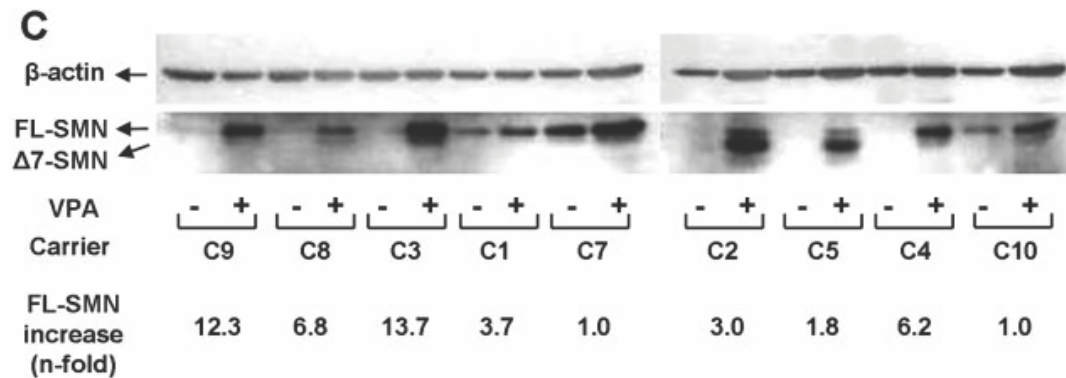
Blood Expression Levels Respond to VPA

Ⓟ Elevated transcript and protein in SMA carriers

1 – 3.4
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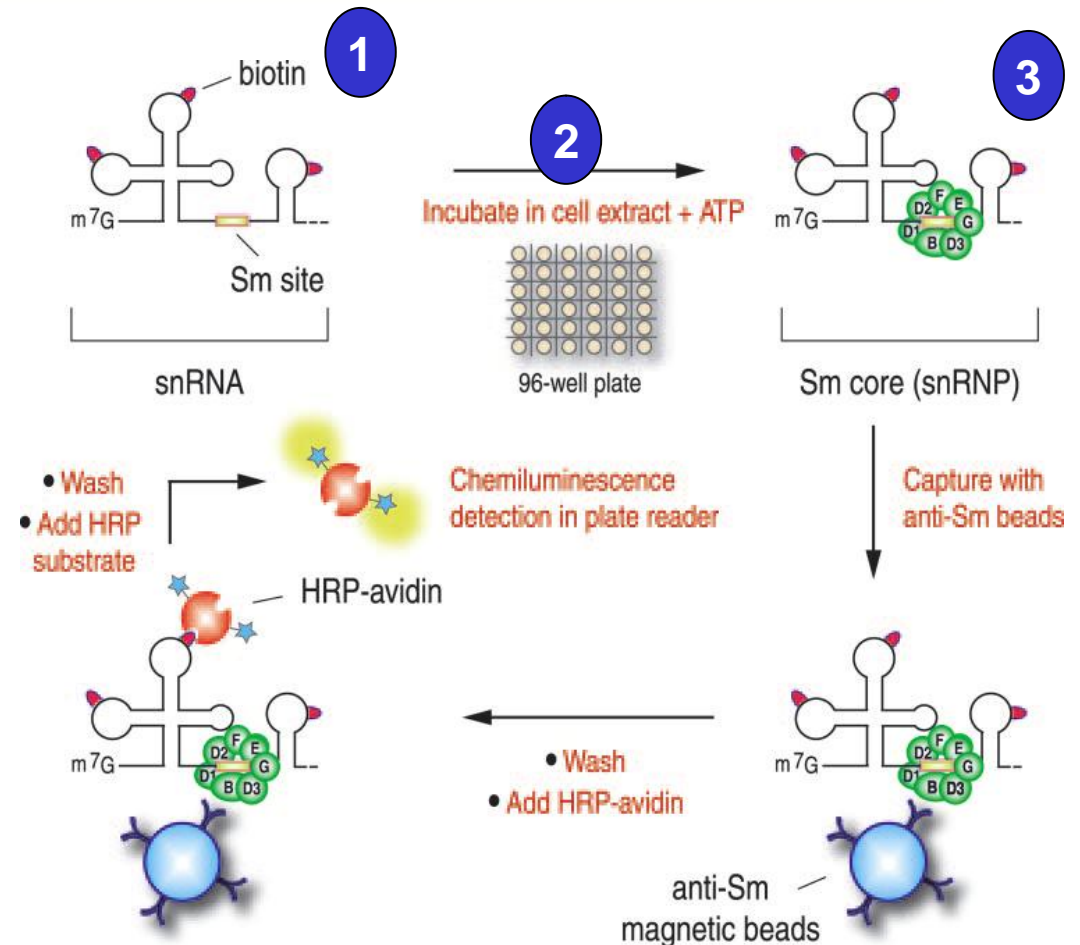
1 – 13.7
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Measuring SMN Activity: snRNP Assembly

- 1) Biotinylated snRNA
- 2) Cell extract
- 3) *de novo* assembly with endogenous core proteins

- p Rate and extent of reaction varies with amount of SMN
- p Could be adapted to blood samples



Caveats

- Ⓟ Does not appear that SMN expression levels in the blood echo the clinical status of patients
 - Ⓝ Correlation is better for Type I than for Type II or III
 - Ⓝ May still be useful to measure a response to drug
- Ⓟ Blood and fibroblast cells are not the target tissue
- Ⓟ Very little information available about SMN expression in human spinal cord tissue of normals or patients – relationship to blood levels not established
- Ⓟ Fragile pediatric population: cannot repeatedly take large blood samples

SMN Biomarker Studies: What's Needed

- Ⓟ Practical, sensitive method for SMN protein
 - Ⓝ ELISA or other protein methods, implemented for multi-center studies
 - Ⓝ Biochemical activity assay may amplify small changes
- Ⓟ Shore up “natural history of SMN”
 - Ⓝ Developmental profile of SMN transcript and protein levels prenatal, perinatal, postnatal timepoints
 - Ⓝ Mechanisms for gene expression regulation in different tissues
 - Ⓝ Correlation of SMN expression in spinal cord vs. elsewhere
 - Ⓟ Cross-sectional or longitudinal study
 - Ⓝ Characterize other SMN activities that may become readouts
 - Ⓝ Recruit additional patients, investigators, sites
- Ⓟ Centralize biomarker database across neuro diseases
 - Ⓝ Neurodegeneration, muscle atrophy markers may also be useful

